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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,852	12/22/2003	Rocco Dean Gogliotti	PC25547A	9086

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WARNER-LAMBERT COMPANY
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EXAMINER

COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 05/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/743,852

Applicant(s)

GOGLIOTTI ET AL.

Examiner

Brenda L. Coleman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>3/04;5/06/04; 5/20/04</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-23 are pending in the application.

Election/Restrictions

1. Applicant's election of Group I in the reply filed on March 15, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 15-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

HOW TO USE: Claims 15-23 are to the composition and method of treating a disorder mediated by PI3K. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. The scope of the method claims are not adequately enabled solely based on its inhibitory effect on PI3K provided in the specification. Diseases and/or disorder(s) suspected to be associated with PI3K include asthma, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and hypertension. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is difficult to treat many of the disorders claimed herein.

No screening protocol(s) are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed benzo[1,4]oxazine compounds. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in-vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.

The specification has no working examples on the use of the substituted benzo[1,4]oxazine. There must be evidence to justify the contention that the claimed compounds can be useful in the treatment of "rheumatoid arthritis, osteoarthritis, inflammatory diseases, autoimmune diseases, cardiovascular diseases,

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atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, coronary artery disease, cancer, breast cancer, glioblastoma, endometrial carcinoma, hepatocellular carcinoma, colon cancer, lung cancer, melanoma, renal cell carcinoma, thyroid carcinoma, small cell lung cancer, squamous cell lung carcinoma, glioma, breast cancer, prostate cancer, ovarian cancer, cervical cancer, leukemia, cell lymphoma, lymphoproliferative disorders, type II diabetes, respiratory diseases, bronchitis, asthma, chronic obstructive pulmonary disease, etc.”.

Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds. *In re Buting* 163 USPQ 689. The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the “cancer” category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

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3. Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

- a) Claims 1-23 are vague and indefinite in that it is not known what is meant by the second occurrence of "or a pharmaceutically acceptable salt thereof".
- b) Claims 1-9, 11, 13 and 15-23 are vague and indefinite in that it is not known what is meant by the moieties $\text{-CH}_2\text{-}$ and $\text{-(CH}_2\text{)}_2\text{-}$, which are included in the moiety $\text{C}_1\text{-C}_3\text{-alkylene}$ in the definition of L.
- c) Claims 1-9, 11, 13 and 15-23 are vague and indefinite in that it is not known what is meant by the moiety -CH=CH- , which is included in the moiety $\text{C}_2\text{-C}_3\text{-alkenylene}$ in the definition of L.
- d) Claims 1-9, 11, 13 and 15-23 are vague and indefinite in that it is not known what is meant by the moiety $\text{-CH}_2\text{-O-}$, which is included in the moiety $\text{-C}_1\text{-C}_3\text{-alkyl-O-}$ in the definition of L.
- e) Claims 1-9, 11, 13 and 15-23 are vague and indefinite in that it is not known what is meant by the moiety $\text{-CH}_2\text{-O-CH}_2\text{-}$, which is included in the moiety $\text{-C}_1\text{-C}_3\text{-alkyl-O-C}_1\text{-C}_3\text{-alkyl}$ in the definition of L.
- f) Claims 1-9, 11, 13 and 15-23 are vague and indefinite in that it is not known what is meant by the moiety $\text{-CH}_2\text{-S-}$, which is included in the moiety $\text{-C}_1\text{-C}_3\text{-alkyl-S-}$ in the definition of L.

- g) Claims 1-3, 5, 6, 8, 9 and 15-23 are vague and indefinite in that it is not known what is meant by the moiety a piperidinyl, which is included in the moiety 3- to 8-membered heterocycloalkyl in the definition of R^6 .
- h) Claims 1-3, 5, 6, 8, 9 and 15-23 are vague and indefinite in that it is not known what is meant by the moieties a 5-isoxazolyl, a 3-isoxazolyl, a 2-thienyl or a 3-thienyl, which are included in the moiety 5-membered heteroaryl in the definition of R^6 .
- i) Claims 1-3, 5, 6, 8, 9 and 15-23 are vague and indefinite in that it is not known what is meant by the moieties a 4-pyridinyl or a 3-pyridinyl, which are included in the moiety 6-membered heteroaryl in the definition of R^6 .
- j) Claims 1-3, 5, 6, 8, 9 and 15-23 are vague and indefinite in that it is not known what is meant by the moiety a 2-quinoxalinyl, which is included in the moiety 8- to 12-membered bicyclic heteroaryl in the definition of R^6 .
- k) Claims 1-3, 5, 6, 8, 9 and 15-23 are vague and indefinite in that it is not known what is meant by the moieties a 1-naphthalenyl or a 2-naphthalenyl, which is included in the moiety 9- to 12-membered bicyclic aryl in the definition of R^6 .
- l) Claims 4, 7 and 11 are vague and indefinite in that it is not known what is meant by the moieties a 1-naphthalenyl or a 2-naphthalenyl, which is included in the moiety a naphthalenyl in the definition of R^6 .
- m) Claim 10 recites the limitation "8-oxo.....octanoic acid methyl ester" in the nomenclature of the third species. There is insufficient antecedent basis for this limitation in the claim.

n) Claim 12 is vague and indefinite in that it is not known what is meant by the nomenclature of the 1st species, which is missing an open bracket.

o) Claims 15-20 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the disorders capable of being treated by modulating the activity of PI3K. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be

given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in cancer, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually

precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

p) Claim 18 is vague and indefinite in that it is not known what is meant by the second occurrence of breast cancer.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1, 4, 5, 18, 22 and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by SUTO et al., U.S. Patent Application Publication 2004/0214872. SUTO teaches the compounds, compositions and method of use of the compounds of the

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instant invention where K is S; Y is C(S); R⁸ is -CH₂-CH₂-CH₂-C(O)OH; R⁷, R⁹ and R¹⁰ are H; W is O; p is 0; E is CH₂; D is CH₂; A is absent; L is absent and R⁶ is CH₃ as shown on page 383, first species in the second column.

5. Claims 1, 4, 5 and 15-23 are rejected under 35 U.S.C. 102(e) as being anticipated by RUCKLE et al., U.S. Patent Application Publication 2004/0092561. RUCKLE teaches the compounds, compositions and method of use of the compounds of the instant invention where K is S; Y is C(O); R⁷, R⁸, R⁹ and R¹⁰ are H; W is O; p is 0; E is CH₂; D is CH₂; A is absent; L is absent and R⁶ is CH₃ as shown in example 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

1. Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over RUCKLE et al., U.S. Patent Application Publication 2004/0092561. The generic structure of RUCKLE encompasses the instantly claimed compounds (see Formula (II) on page 8) and for the same uses as claimed herein. Example 11, which anticipates the compounds of the instant invention differ only in the substituents Y¹, Z, R¹, R², R⁴ and n. Page 7, paragraphs [0084] through [0088] defines the substituents Y¹, Z, R¹, R², R⁴ and n as follows: Y¹ is S, O or NH; Z is S or O; R¹ is selected from the group comprising or consisting of H, CN, carboxy, acyl, C₁-C₆ alkoxy, halogen, hydroxyl,

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acyloxy,; R² is selected from the group comprising or consisting of H, halogen, acyl, amino, an unsubstituted or substituted C₁-C₆ alkyl,; n is 0 to 2 and pages 8 paragraph [0117] is selected from the group comprising or consisting of H, acyl, unsubstituted or substituted C₁-C₆ alkyl, an unsubstituted or substituted C₂-C₆ alkenyl..... The compounds of the instant invention are generically embraced by RUCKLE in view of the interchangeability of the substitutions of the benzo[1,4]oxazine ring. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example ethyl or propyl as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

Additionally, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the instantly claimed isomer for the known (5Z)-5-[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)methylene]-1,3-thiazolidene-2,4-dione, etc. of RUCKLE as well as the methyl. Such modification would be obvious because such structurally related compounds suggest one another and would be expected to share common properties absent a showing of unexpected results. (See *In re Norris*, 84 USPQ 459, on the obviousness of structural isomers).

Claim Objections

6. Claim 21 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be stated in the alternative.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Brenda L. Coleman
Primary Examiner Art Unit 1624
May 25, 2006